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14. ABSTRACT

The overall goal of the study is to examine whether altered vitamin D status (as measured by serum metabolites and by functional polymorphisms with genes related to vitamin D transport, metabolism and activity) is associated with increased risk of aggressive prostate cancer, and may explain some of the racial disparity seen in aggressive prostate cancer. The project activities, as outlined in the Statement of Work Tasks and Milestones, are running on schedule. The study team has been organized and participates in monthly conference calls (or more frequent as needed) to discuss study progress and data collection and analyses, IRB approval was obtained from all local institutions and the DoD HSRRB. Biospecimens have been shipped to two of the institutions and measurements of circulating concentrations of vitamin D metabolites, calcium and phosphorus are complete. Data has been requested and obtained from the parent study, PCaP. Data merging, clearing and analyses are underway. With large representation of African Americans in this investigation, the proposed research has tremendous potential to provide insights into a chronically underserved population carrying an unequal burden of disease.

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Vitamin D, prostate cancer aggressiveness, polymorphisms, racial disparities

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INTRODUCTION:

Experimental and ecologic studies support a role of vitamin D in prostate cancer prevention and prognosis; however, epidemiologic study results are inconsistent. Altered vitamin D status (as measured by serum metabolites and by functional polymorphisms within genes related to vitamin D transport, metabolism and activity) is hypothesized to be associated with increased risk of aggressive prostate cancer, and may explain some of the racial disparity seen in aggressive prostate cancer. It is also hypothesized that plasma parathyroid hormone (PTH), serum calcium and serum phosphorus levels are inversely and directly correlated with serum 25(OH)D and $1,25(OH)_2D$ levels, respectively, and are positively associated with disease aggressiveness. Polymorphisms within *VDR, CYP24A1, CYP27B1, DBP* and *CYP2R1* will be examined to determine whether 1) allele and genotype frequencies differ by race, 2) serum vitamin D metabolite concentrations are related to polymorphisms in these genes, 3) allele and genotype/haplotype frequencies are different in more aggressive disease as compared to less aggressive disease, and 4) vitamin D and genetic polymorphisms act synergistically to affect prostate cancer aggressiveness. We will examine these associations among vitamin D status, PTH, calcium, phosphorus, polymorphisms in vitamin D-related genes, and prostate cancer aggressiveness in the North Carolina-Louisiana Prostate Cancer Project (PCaP), a previously-conducted case-only study of prostate cancer among equal numbers of African Americans and European Americans. New laboratory data will be generated using previously-collected biospecimens from PCaP, and data will be analyzed using epidemiologic techniques for estimating odds of highly aggressive prostate cancer according to vitamin D, PTH, calcium, phosphorus and genetic polymorphisms.

BODY:

The project activities, as outlined in the Statement of Work (SOW) Tasks and Milestones, are running on schedule. The majority of the activities in Task #1 to occur in the first six months of the grant award period have been accomplished. Activities related to Task #2 were planned to occur in months 7 to 24 of the grant award period. Several of these have already been accomplished as noted in the list below, and others are underway and are expected to be accomplished in Year 2 as originally planned. Below please find the original SOW activity listed in the numbered bullet, and the progress and status of those activities listed in the indented lettered bullet underneath each activity.

Task 1: Run-in Phase, Months 1-6:

1. Organize the investigative team and schedule regular conference calls between investigators
    a. Conference calls have been occurring every month
2. Obtain IRB approval for the study from all institutions and DoD HSRRB
    a. IRB approval was granted by each of the institutions (USC, Roswell Park Cancer Institute, UCLA, and UNC-CH) and by DoD HSRRB
3. Complete the data acquisition form from the parent PCaP Study
    a. Data was requested and obtained from PCaP
4. Develop a Manual of Operations (MOP), a detailed document describing data transfer, data merging, and data management systems. The MOP content is based on our successful experience with other large-scale epidemiologic studies.

   a. A system of data transfer has been developed. The MOP has been assembled and is under development.
5. Arrange for shipment of 1,200 serum to Roswell Park for vitamin D analyses, 1,200 plasma and 1,200 DNA samples to USC for PTH analyses and genotyping, and serum samples to UCLA for calcium (1,200 samples) and phosphorus (1,200 samples) analyses
   a. It was decided that plasma samples were more appropriate for vitamin D analyses, instead of serum samples, because the plasma samples were collected and transported under light-protected conditions.
   b. Plasma samples were shipped from UNC-CH to Roswell Park and serum samples were shipped UCLA
   c. A biospecimen request for plasma to be shipped to USC for PTH analyses was submitted
   d. DNA samples have not been shipped yet as we are determining the best lab and method for conducting the genotyping before requesting those specimens.
6. Drs. Steck and Johnson attend PCRP IMPaCT Annual Meeting or other scientific meeting.
   a. There was not an IMPaCT meeting in Year 1. Dr. Steck attended the American Society of Preventive Oncology meeting in March 2012.

All milestones for Task #1 were met (IRB and HSRRB approval, samples aliquotted and shipped to labs, data systems in place for capture of all data from different sources), with the exception that plasma samples have not been sent to USC for PTH analyses yet, and DNA has not been shipped for genotyping.

Task 2: Laboratory Analyses, Interim Data Analyses, Months 7-24:

1. Conduct plasma 25(OH)D and 1,25$(OH)_2$D lab measurements at Roswell Park Cancer Institute
   a. Plasma vitamin D metabolite measurements are complete.
2. Conduct genotyping at Environmental Genomics Core at USC
   a. This will occur in Year 2. We are developing the list of SNPs and determining the best genotyping technique for genotyping the list of SNPs of interest. A preliminary list of tagSNPs in five genes of interest has been developed, and is being compared with the literature to ensure appropriate coverage of both the variability in each gene, as well as evidence supporting an association between individual SNPs and prostate cancer in previous studies.
3. Conduct plasma PTH measurements at Psychoneuroimmunology Lab at USC
   a. This will occur in Year 2
4. Conduct serum calcium and phosphorus measurements at UCLA
   a. Serum calcium and phosphorus measurements are complete.
5. Hire graduate assistant at USC
   a. A senior-level doctoral Student, Mr. Fred Tabung, has been hired as a GA.
6. Have all raw data sent to USC and to PCaP parent study
   a. Raw data from Roswell Park and UCLA have been distributed to USC. Data generated from the study will be sent to PCaP at the end of the study.
7. Manage data, begin cleaning data as it becomes available
   a. Data from PCaP, Roswell Park, and UCLA have been merged and cleaned.
8. Drs. Steck and Johnson attend PCRP IMPaCT Annual Meeting or other scientific meeting.
   a. This will occur in Year 2.

Half of the milestones for Task #2 (successful completion of lab work and raw data deposit at centralized location) have been completed in that half of the laboratory assays are completed and the data have been distributed to USC for data cleaning and analyses. The measurement of PTH and the genotyping will be conducted in Year 2. Submission of an abstract to a scientific meeting and subsequent manuscript submission in Year 2 are in development.

KEY RESEARCH ACCOMPLISHMENTS:

- Obtained IRB approval for the study from all institutions and DoD HSRRB.
- Developed a system of data transfer.
- Arranged for shipment of plasma samples to Roswell Park for vitamin D analyses and serum samples to UCLA for calcium and phosphorus analyses.
- Conducted plasma 25(OH)D and $1,25(OH)_2D$ lab measurements (by Roswell Park Cancer Institute).
- Conducted serum calcium and phosphorus measurements (by UCLA).
- Hired graduate assistant at USC.
- Obtained data from parent study (PCaP) and began merging and cleaning data.

REPORTABLE OUTCOMES:

As Year 1 primarily involved organizing the study team, IRB application and approval, and arrangement for shipment of samples, there are no reportable outcomes in Year 1.

CONCLUSION:

The project is proceeding on schedule. Data are currently being collected and analyzed, and we are determining the optimal strategy for selecting SNPs and genotyping to provide the most robust genetic data related to vitamin D activity and metabolism. Presentation of preliminary findings at a scientific meeting is planned for Year 2. With the large representation of African Americans in this investigation, the proposed research has tremendous potential to provide insights into a chronically underserved population carrying an unequal burden of disease. By examining modifiable biomarkers of risk of aggressive disease and genetic susceptibility by race, this study will impact the identification of subjects at high risk for advanced disease and aid in the design of interventions to target those individuals who will receive the most benefit.